EXHIBIT J

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of:	T. BARBERICH et al.	
Application No.:	09/527,844	Group Art Unit: 1617
Filed:	March 17, 2000	Examiner: M. Bahar
For:	METHODS FOR THE TREATMENT OF NEUROLEPTIC AND RELATED DISORDERS USING ZIPRASIDONE METABOLITES	Attorney Docket No: 4821-334-999

RESPONSE

Assistant Commissioner for Patents

Washington, D.C. 20231

Sir:

In response to the Office Action dated November 5, 2002, please consider and enter the following remarks into the file of the above-captioned application. A Petition for Extension of Time, with the provision for required fee, is enclosed herewith.

AMENDMENTS

Please amend claim 5 to provide the following:

5. (Amended) The method of claim 1 wherein the ziprasidone metabolite is ziprasidone sulfoxide or ziprasidone sulfone.

Please add the following new claims:

50. (New) A method of treating or prophylaxis of a neuroleptic disorder in a patient which comprises administering to a patient in need of such treatment or prophylaxis a therapeutically effective amount of ziprasidone sulfoxide, or a pharmaceutically acceptable salt, solvate, hydrate, or clathrate thereof.

51. (New) The method of claim 50 wherein the neuroleptic disorder is psychosis, an affective disorder, or anxiety.

52. (New) A method of treating or prophylaxis of a neuroleptic disorder in a patient which comprises administering to a patient in need of such treatment or prophylaxis a therapeutically effective amount of ziprasidone sulfone, or a pharmaceutically acceptable salt, solvate, hydrate, or clathrate thereof.

53. (New) The method of claim 52 wherein the neuroleptic disorder is psychosis, an affective disorder, or anxiety.

REMARKS

Claims 1-15 and 50-53 are pending in this application. A marked-up copy of the amended claims is attached hereto as Appendix A. No new matter has been introduced.

Rejections under 35 U.S.C. §§ 102 and 103 are maintained in this Office Action. Applicants respectfully request the withdrawal of these rejections for the reasons set forth below.

The Rejection Under 35 U.S.C. § 102 Should be Withdrawn

On page 2 of the Office Action, claims 1-4 and 6-9 are rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Davis *et al.*, CNS Drugs, 8(2):153-159 (1997) ("Davis"). In particular, it is alleged in the Office action that because Davis discloses ziprasidone as an antipsychotic drug having a high affinity for serotonin 5-HT_2 and dopamine D_2 receptors, and because ziprasidone is shown to be effective in treating depression associated with schizophrenia, the invention as recited in claim 1-4 and 6-9 is anticipated by Davis. Office Action, page 2, lines 12-15. This rejection is respectfully traversed.

As the Examiner is aware, a prior art reference must disclose all the elements of a claim in order to anticipate the invention recited by that claim. *Manual of Patent Examining Procedure* (MPEP) § 2131. There must be no difference between the claimed invention and the reference disclosure as viewed by one of ordinary skill in the art. *Scripps Clinic & Research Fdn. v. Genentech*, 927 F.2d 1565, 1576 (Fed. Cir. 1991). Put another way, "[a] claim is anticipated and therefore invalid only when a single prior art reference discloses each and every limitation of the claim." *Glaxo Inc. v. Novapharm Ltd.*, 52 F.3d 1043, 1047, cert. denied, 116 S. Ct. 516 (1995) (citations omitted) (emphasis added).

In the event a reference does not explicitly teach all elements of a claim, anticipation can only be shown by inherency if, and only if, the cited reference makes it clear that the missing descriptive matter is necessarily present in the thing described in the

reference and that it would be so recognized by one of ordinary skill in the art. *In re Robertson*, 169 F.3d 743, 49 U.S.P.Q.2d 1949 (Fed. Cir. 1999) (citing *Continental Can Company USA Inc. v. Monsanto Company*, 948 F.2d 1264 (Fed. Cir. 1991)). Consequently, inherency cannot be established by probabilities or possibilities: "[t]he mere fact that a certain thing may result from a given set of circumstances is not sufficient to support an assertion of inherency." *In re Oelrich*, 212 U.S.P.Q. 323, 326 (C.C.P.A. 1981) (quoting *Hansgirg v. Kemmer*, 102 F.2d 212, 414 (C.C.P.A. 1939)). Therefore "[i]n relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." MPEP § 2112, citing *Ex parte Levy*, 17 U.S.P.Q.2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in the original).

Davis does not disclose each and every element of the claimed invention. As admitted in page 3 of the Office Action, Davis does not explicitly disclose metabolites of ziprasidone. However, it is alleged in the Office Action that "the administration of ziprasidone necessarily and inherently results in its administration/conversion to ziprasidone metabolites in vivo." Applicants respectfully submit that this assertion, which incorrectly characterizes Davis, is based upon what appears to be a fundamental misunderstanding of the claimed invention.

The claims pending in this application recite methods of treatment and prophylaxis comprising administering a ziprasidone metabolite to a patient. The claims use the term "administering" in a manner entirely consistent with its conventional meaning, *e.g.*, "to apply as a remedy." *The American Heritage College Dictionary*, 17 (3rd ed., 1997). In other words, a compound that exists outside of the patient is given, or applied, to the patient. The Examiner's assertion that the *in vivo* conversion of ziprasidone into its metabolites constitutes "administration" is entirely contrary to the term's well understood meaning. The assertion is also contrary to the way in which the term is used in the specification of this application. For example, the specification describes dosage forms (*e.g.*, tablets and capsules) of ziprasidone metabolites that can be used in methods of the invention. *See, e.g.*, specification, page 7, lines 16-23. The disclosure of dosage forms presupposes the existence of a ziprasidone metabolite prior to its administration to a patient.

In sum, Davis does not disclose the administration of a ziprasidone metabolite to a patient, much less the administration of a ziprasidone metabolite to a patient in an amount sufficient to treat or prevent a disease. For the reason, Applicants respectfully request that the rejection of the claims under § 102 be withdrawn.

The Rejections Under 35 U.S.C. § 103 Should Be Withdrawn

On pages 2-4 of the Office Action, claims 1-15 are rejected under 35 U.S.C. § 103 as allegedly obvious over Davis in view of U.S. Patent No. 4,831, 031 to Lowe *et al.* ("Lowe") and U.S. Patent No. 5,312,925 to Allen *et al.* ("Allen"). In particular, it is alleged that although Davis does not disclose metabolites of ziprasidone, the claimed invention is obvious because Lowe discloses a genus of compounds that encompasses ziprasidone and their pharmaceutically acceptable salts and Allen discloses the use of ziprasidone hydrochloride as a neuroleptic agent. Applicants respectfully traverse this rejection.

As the Examiner is well aware, prior art references used to establish a *prima facie* case of obviousness must teach or suggest all of the claim limitations, and there must be some suggestion or motivation to modify or combine the cited references. MPEP § 2143. None of the cited references disclose or suggest a ziprasidone metabolite, much less the administration of a ziprasidone metabolite for the treatment or prevention of disease. Moreover, even if one were to assume, for the sake of argument, that the cited references do suggest the use of ziprasidone metabolites, they would not have provided those of ordinary skill in the art with any motivation to attempt the claimed invention. This is because the art, prior to this invention, taught that ziprasidone metabolites are inactive; *i.e.*, that the pharmacological activity of ziprasidone is due to ziprasidone itself, not to its metabolites. *See, e.g.*, Ereshefsky, *J. Clin. Psychiatry*, 57 (Suppl. 11): 12-25 (1996) at page 14, Table 3, a copy of which is enclosed herewith. For these reasons, Applicants respectfully request that the rejection of under § 103 be withdrawn.

It is well established that a *prima facie* case of obviousness must be based on factual and objective evidence found in prior art. *See In re Sang-Su Lēē*, 277 F.3d 1338, 1343-4 (Fed Cir. 2002). Yet the rejections set forth in the Office Action are based entirely on assertions devoid of factual support, such as the assertions that the term "administration" encompasses *in vivo* formation and that "the employment of ziprasidone metabolites would result in the same *in vivo* activity" as the employment of ziprasidone itself. Office Action, page 4. Citing *Zenith Laboratories Inc. v. Bristol-Myers Squibb Co.*, 30 U.S.P.Q.2d 1285 (Fed. Cir. 1994), the Examiner further alleges that "the Skilled Artisan would know that the compound Ziprasidone is not limited to 'its pre-ingested form'." Applicants respectfully disagree with each of these assertions.[1]

[1] To the extent these assertions are based on the Examiner's personal knowledge, Applicants respectfully request that such knowledge be supported by an affidavit. 37 C.F.R. § 1.104(d)(2).

First, as discussed above, none of the cited references disclose a ziprasidone metabolite, much less the administration of a ziprasidone metabolite to a patient. Second, the assertion that "the employment of ziprasidone metabolites would result in the same *in vivo* activity" is without scientific foundation. In order for the administration of a ziprasidone metabolite to result in the same *in vivo* activity as the administration of ziprasidone itself, ziprasidone itself must be inactive, which is not the case. *See Physician's Desk Reference*, p. 2688 (56th ed., 2002) a copy of which is enclosed herewith. In other words, unless 100 % of the ziprasidone administered to every patient converts into ziprasidone metabolites with identical pharmacological activities, and the activity associated with the administration of ziprasidone comes exclusively from these metabolites, the ziprasidone cannot result in the same *in vivo* activity as its metabolites. As evidenced by the literature, such is not the case. Finally, *Zenith* provides no evidence of what was known prior to this invention about the biological activity of ziprasidone or its metabolites. Indeed, that case concerned a crystalline form of an entirely different drug, and did not concern metabolites at all.[2]

In sum, Applicants respectfully submit that none of the cited references disclose or suggest the administration of ziprasidone metabolite to a patient. For this reason, the rejection of the claims under § 103 should be withdrawn.

[2] Applicants respectfully submit that the Examiner's reliance on *Zenith* is misplaced for other reasons. In particular, *Zenith* concerned whether an *in vivo* conversion of a compound into a patented hydrated form of that compound would constitute an infringement of a patent, not whether the claims of the patent were anticipated or obvious.

CONCLUSION

For the foregoing reasons, Applicants respectfully submit that all of the claims are in condition for allowance.

No fee is believed to be due for this submission. However, should any fees be required, please charge such fees to Pennie & Edmonds LLP Deposit Account No. 16-1150.

Respectfully submitted,

Date: April 4, 2003

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Appendix A

Marked-Up Copy of Amendments to Claims

5. (Amended) The method of claim 1 [or 3] wherein the ziprasidone metabolite is ziprasidone sulfoxide or ziprasidone sulfone.

50. (New) A method of treating or prophylaxis of a neuroleptic disorder in a patient which comprises administering to a patient in need of such treatment or prophylaxis a therapeutically effective amount of ziprasidone sulfoxide, or a pharmaceutically acceptable salt, solvate, hydrate, or clathrate thereof.

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